Memorial Cancer Institute
MEMORIAL REGIONAL HOSPITAL | MEMORIAL HOSPITAL WEST
MEMORIAL AVENTURA GROUP

MANAGEMENT OF RELATED ADVERSE EVENTS IN PATIENTS TREATED WITH ALK,BTK AND IDH1/2 INHIBITOR THERAPY

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Stronger Together

Learning Objectives

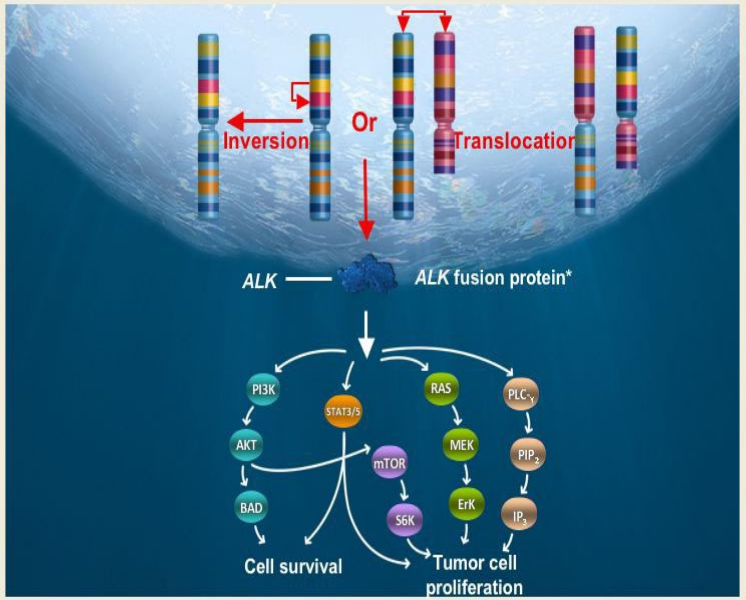
At the end of the presentation the learner will be able to:

Discuss the toxicities and management issues associated with the ALK, BTK AND IDH1/2 Inhibitor Therapy

ALK POSITIVE IN NSCLC

- ALK rearrangements
- Discovered in 2007
- Present 3-5% NSCLC.
- Resulted from alteration in the short arm of chromosome 2, joining the exons 1-13of the EML4-ALK gene to exons 20-29 of ALK gene.
- Young age.
- Non-smoking history.
- Adenocarcinoma of the lung histology.

ALK Pathway



*Subcellular localization of the ALK fusion protein is thought to occur in the cytoplasm, but it is not confirmed.

With permission from Bang Y et al. *Proc ASCO* 2010;Abstract 3.

ALK tyrosine kinase inhibitors (TKIs)

- First generation:
  - Crizotinib
- Second generation:
  - Ceritinib
  - Alectinib
  - Brigatinib
- Third generation:
  - Lorlatinib

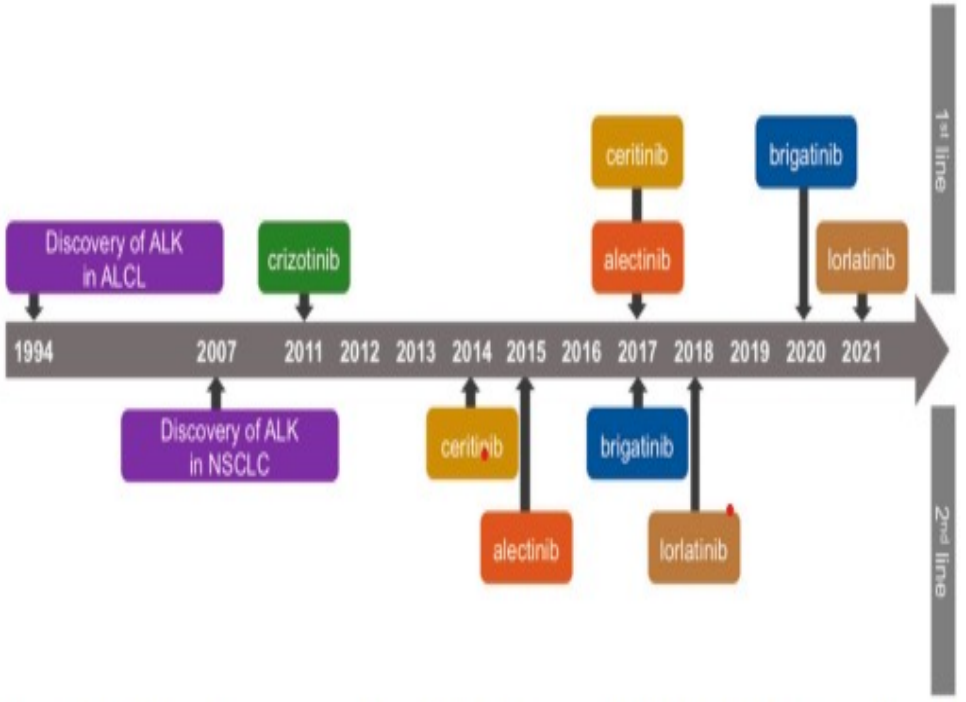
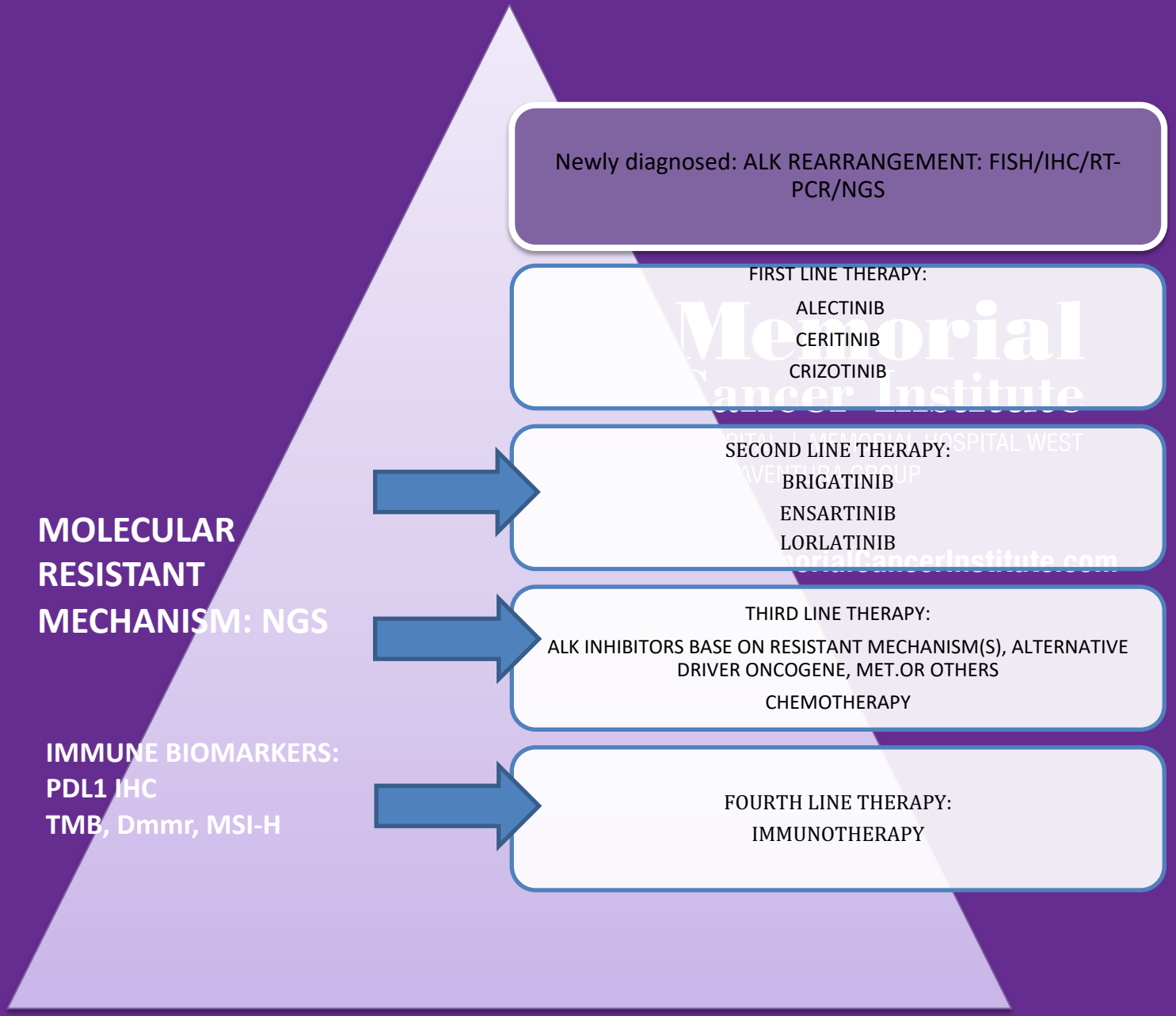


Figure 1. Timeline of discovery of ALK and US FDA approval of ALK-TKIs. ALCL: anaplastic large cell lymphoma, NSCLC: non-small cell lung cancer.

ALK + IN NSCLC


Newly diagnosed: ALK REARRANGEMENT: FISH/IHC/RT-PCR/NGS
FIRST LINE THERAPY:
ALECTINIB
CERITINIB
CRIZOTINIB
SECOND LINE THERAPY:
BRIGATINIB
ENSARTINIB
LORLATINIB
MOLECULAR RESISTANT MECHANISM: NGS
THIRD LINE THERAPY:
ALK INHIBITORS BASE ON RESISTANT MECHANISM(S), ALTERNATIVE DRIVER ONCOGENE, MET.OR OTHERS
CHEMOTHERAPY
IMMUNE BIOMARKERS:
PDL1 IHC
TMB, Dmmr, MSI-H
FOURTH LINE THERAPY:
IMMUNOTHERAPY

FIRST GENERATION: Crizotinib

Crizotinib

Main adverse events:

Visual disturbances 71% (diplopia, photophobia, and blurred vision).

Gastrointestinal disorders: diarrhea occurred in 61% and nausea in 59% of patients.

Edema 49%

The most frequent grade 3–4 adverse events were neutropenia (15%), elevated transaminases (14%), and pulmonary embolism (8%)

EKG as baseline.

Table 3. Adverse Events from Any Cause in the As-Treated Population.*

Adverse Event	Crizotinib (N=171)		Chemotherapy (N=169)†	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Higher frequency in crizotinib group				
Vision disorder‡	122 (71)	1 (1)	16 (9)	0
Diarrhea	105 (61)	4 (2)	22 (13)	1 (1)
Edema§	83 (49)	1 (1)	21 (12)	1 (1)
Vomiting	78 (46)	3 (2)	60 (36)	5 (3)
Constipation	74 (43)	3 (2)	51 (30)	0
Elevated aminotransferases§	61 (36)	24 (14)	22 (13)	4 (2)
Upper respiratory infection§	55 (32)	0	21 (12)	1 (1)
Abdominal pain§	45 (26)	0	20 (12)	0
Dysgeusia	45 (26)	0	9 (5)	0
Headache	37 (22)	2 (1)	25 (15)	0
Pyrexia	32 (19)	0	18 (11)	1 (1)
Dizziness§	31 (18)	0	17 (10)	2 (1)
Pain in extremity	27 (16)	0	12 (7)	0
Higher frequency in chemotherapy group				
Fatigue	49 (29)	5 (3)	65 (38)	4 (2)
Neutropenia§	36 (21)	19 (11)	51 (30)	26 (15)
Stomatitis§	24 (14)	1 (1)	34 (20)	2 (1)
Asthenia	22 (13)	0	41 (24)	2 (1)
Anemia§	15 (9)	0	54 (32)	15 (9)
Leukopenia§	12 (7)	3 (2)	26 (15)	9 (5)
Thrombocytopenia§	2 (1)	0	31 (18)	11 (7)
Similar frequency in the two treatment groups				
Nausea	95 (56)	2 (1)	99 (59)	3 (2)
Decreased appetite	51 (30)	4 (2)	57 (34)	1 (1)
Cough§	39 (23)	0	33 (20)	0
Neuropathy§	35 (20)	2 (1)	38 (22)	0
Dyspnea§	30 (18)	5 (3)	26 (15)	4 (2)

* Adverse events are listed here if they were reported in 15% or more of patients in either treatment group; rates were not adjusted for differences in treatment duration. Higher frequency indicates a difference of 5 percentage points or more between groups; similar frequency indicates a difference of less than 5 percentage points between groups.
† Only events that occurred before crossover to crizotinib are included.
‡ The category of vision disorder comprised a cluster of adverse events including (in descending order of frequency in the crizotinib group) visual impairment, photopsia, blurred vision, vitreous floaters, reduced visual acuity, diplopia, and photophobia.
§ This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.

Crizotinib:
Categorizing side effects

GI

1.Abdominal pain

2. Diarrhea

3. Constipation

4. Vomiting

Diarrhea/Management:

1.. Target therapy teaching

2. May appear first 2 weeks after therapy

3. To take loperamide with diarrhea #1 (2 tablets each episode/no more than 10 daily)

4. If loperamide does not help to add Diphenoxylate and atropine 2 tablets x 4 times

5. Prevent to get dehydrated

6. Dietary recommendations

Constipation/ Management:

1. Increased fluid intake

2. Recommended exercise

3. Drink prum juice

4. Take surfactans (docusate socium), stimulant laxative (senna), etc

Vomiting:

1. Try ginger

2. Treat with 5-HT3 antagonist (ondasetron)

Visual impairment:

1. To be seen by ophthalmologist

2. If affecting ADL's we should make dose reduction

Headaches:

1. Recommended OTC medications : aleve/tylenol

Labs:

Elevated LFT's x3, dose reduction

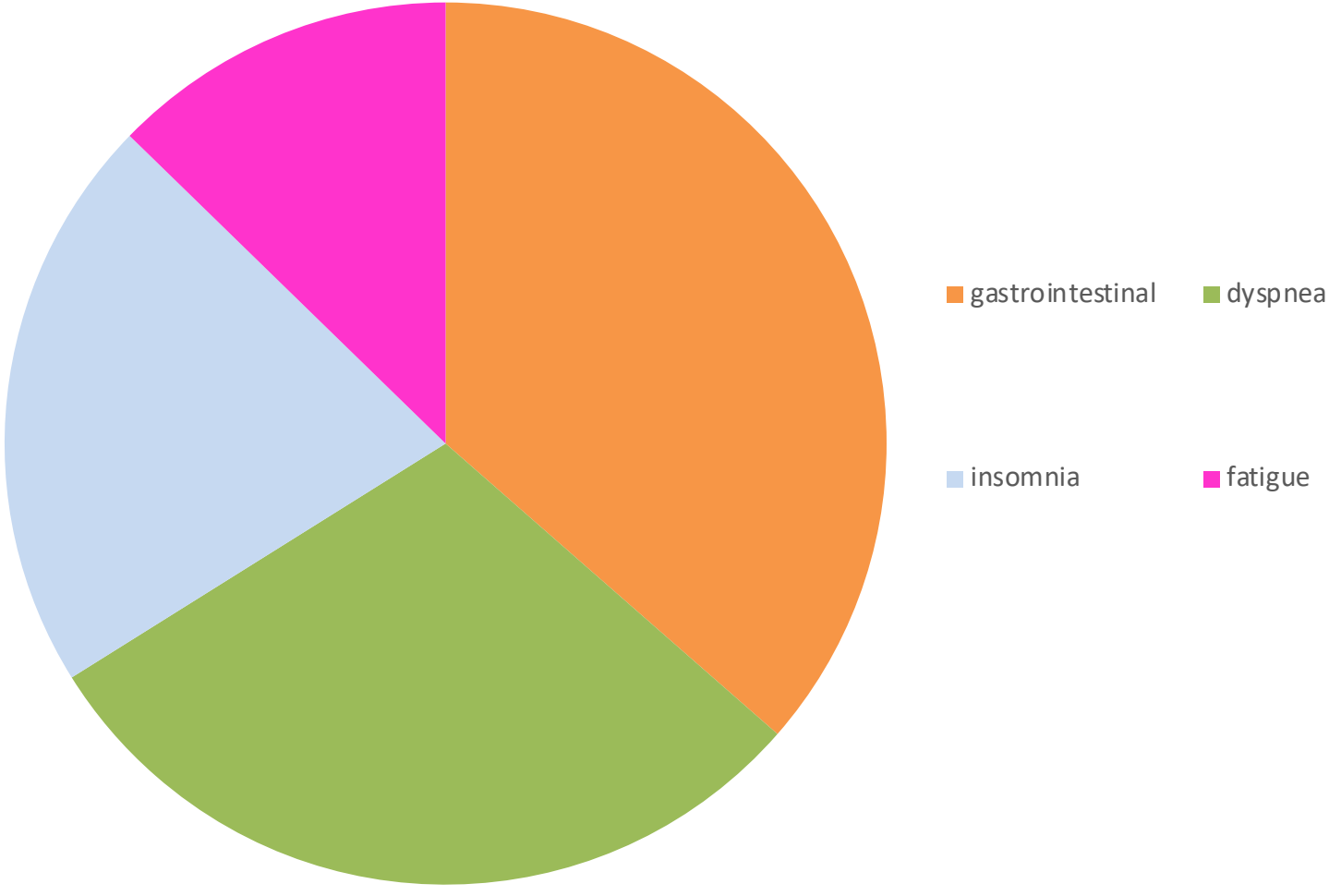
Physical symptoms:

Peripheral Edema

Summary:

1. The most frequent adverse events were mild and moderate gastrointestinal events and mild visual disturbances

Crizotinib Adverse Events



Ceritinib

Main adverse events:

Hepatic disorders: increased ALT in 60% (grades 3–4: 31%).

Gastrointestinal: Diarrhea o 85% (grades 3–4: 5%), nausea 69% (grades 3–4: 3%), vomiting 66% (grades 3–4: 5%),

EKG as baseline.

Table 4. All-Causality Adverse Events Occurring in Greater Than 15% (Any Treatment Arm) in Patients With *ALK*-Positive NSCLC (Safety Set, n = 304)

	Ceritinib 450-mg Fed n = 108		Ceritinib 600-mg Fed n = 86		Ceritinib 750-mg Fasted n = 110	
Preferred Term	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Diarrhea	62 (57.4)	1 (0.9)	56 (65.1)	2 (2.3)	87 (79.1)	10 (9.1)
Vomiting	42 (38.9)	2 (1.9)	48 (55.8)	1 (1.2)	70 (63.6)	4 (3.6)
Nausea	45 (41.7)	0	48 (55.8)	5 (5.8)	63 (57.3)	6 (5.5)
Alanine aminotransferase increased	44 (40.7)	19 (17.6)	41 (47.7)	25 (29.1)	45 (40.9)	25 (22.7)
Aspartate aminotransferase increased	38 (35.2)	8 (7.4)	33 (38.4)	14 (16.3)	41 (37.3)	11 (10.0)
Gamma-glutamyltransferase increased	36 (33.3)	24 (22.2)	23 (26.7)	17 (19.8)	26 (23.6)	15 (13.6)
Fatigue	24 (22.2)	1 (0.9)	27 (31.4)	2 (2.3)	30 (27.3)	5 (4.5)
Abdominal pain	22 (20.4)	0	24 (27.9)	1 (1.2)	32 (29.1)	2 (1.8)
Decreased appetite	20 (18.5)	0	23 (26.7)	1 (1.2)	27 (24.5)	3 (2.7)
Cough	25 (23.1)	0	15 (17.4)	0	24 (21.8)	1 (0.9)
Abdominal pain upper	20 (18.5)	0	11 (12.8)	1 (1.2)	27 (24.5)	0
Blood creatinine increased	23 (21.3)	0	15 (17.4)	0	17 (15.5)	0
Headache	17 (15.7)	2 (1.9)	13 (15.1)	2 (2.3)	25 (22.7)	2 (1.8)
Pyrexia	11 (10.2)	1 (0.9)	18 (20.9)	1 (1.2)	23 (20.9)	1 (0.9)
Weight decreased	14 (13.0)	0	16 (18.6)	1 (1.2)	17 (15.5)	1 (0.9)
Blood alkaline phosphatase increased	20 (18.5)	5 (4.6)	10 (11.6)	3 (3.5)	16 (14.5)	5 (4.5)
Constipation	11 (10.2)	0	15 (17.4)	0	16 (14.5)	0
Dyspnea	14 (13.0)	1 (0.9)	15 (17.4)	2 (2.3)	12 (10.9)	4 (3.6)
Back pain	14 (13.0)	1 (0.9)	9 (10.5)	0	17 (15.5)	2 (1.8)
Hyperglycaemia	13 (12.0)	8 (7.4)	9 (10.5)	5 (5.8)	17 (15.5)	10 (9.1)
Noncardiac chest pain	11 (10.2)	0	9 (10.5)	0	17 (15.5)	0
Asthenia	10 (9.3)	1 (0.9)	19 (22.1)	3 (3.5)	7 (6.4)	2 (1.8)

ALK, ALK receptor tyrosine kinase.

Ceritinib : Categorizing side effects

GASTROINTESTINAL IMPAIRMENT:

1.Abdominal pain

2. Diarrhea

3. Constipation

4. Vomiting

Diarrhea/Management:

1.. Target therapy teaching

2. May appear first 2 weeks after therapy

3. To take loperamide with diarrhea #1 (2 tablets each episode/no more than 10 daily)

4. If loperamide does not help to add Diphenoxylate and atropine 2 tablets x 4 times

5. Prevent to get dehydrated

6. Dietary recommendations

Constipation/ Management:

1. Increased fluid intake

2. Recommended exercise

3. Drink prune juice

4. Take surfactants (docusate sodium), stimulant laxative (Senna), etc

Vomiting:

1. Try ginger

2. Treat with 5-HT3 antagonist (ondasetron)

Cardiac impairment:

1. May cause QT interval prolongation.

Management:

Monitor EKG and electrolytes

1. EKG as baseline

2. Electrolytes every 4 weeks

Elevated Liver Enzymes:

To check LFT's once a month

Labs:

CBC and CMP :

Check liver enzymes every 4 weeks.

Check electrolytes

Diagnostics:

EKG as baseline

Repeat if patient is symptomatic

Ceritinib

Table 3. Recommendations for dose modifications for ceritinib-related adverse events.[44]

Toxicity	Monitoring parameters	Criteria for dose modification	Dose modification
Cardiac QTc prolongation	Periodic ECGs and electrolytes in patients with CHF, bradyarrhythmias, electrolyte abnormalities, concurrent QTc-prolonging therapy	QTc >500 ms, with ≥2 separate ECGs	Withhold ceritinib until QTc <481 ms or returns to baseline Resume ceritinib with 150 mg dose reduction if baseline QTc ≥481 ms Discontinue ceritinib indefinitely
		QTc prolongation with torsades de pointes, polymorphic ventricular tachycardia, or serious arrhythmia	
Bradycardia	Regularly monitor for HR <50 bpm and blood pressure	Symptomatic non-life-threatening bradycardia	Withhold ceritinib until symptoms resolve or HR ≥60 bpm Evaluate for concurrent medications that can cause bradycardia Adjust dose of ceritinib accordingly
		Significant bradycardia requiring clinical intervention or life-threatening bradycardia in patients also taking medication that can cause bradycardia or hypotension	Withhold ceritinib until symptoms resolve or HR ≥60 bpm Resume ceritinib with 150 mg dose reduction if concomitant bradycardia- or hypotension-causing medication cannot be adjusted or stopped
		Life-threatening bradycardia in patients without concurrent medication that can cause bradycardia or hypotension	Discontinue ceritinib indefinitely
Endocrine Hyperglycemia	Serum glucose	Persistent BG >250 mg/dL despite optimal management with antihyperglycemics	Withhold ceritinib until hyperglycemia is adequately controlled Resume ceritinib with 150 mg dose reduction Discontinue ceritinib if adequate hyperglycemia control cannot be achieved
Gastrointestinal Diarrhea, nausea, vomiting	Frequency of diarrhea, nausea, or vomiting; weight; electrolytes	Symptoms persist despite optimal management with antidiarrheals or antiemetics or become severe or intolerable	Withhold ceritinib until symptoms improve Resume ceritinib with 150 mg dose reduction
Hepatic Elevated LFTs	LFTs monthly; more frequently with elevated ALT or AST	ALT ≥5 × ULN or AST ≥5 × ULN and total bilirubin ≤2 × ULN	Withhold ceritinib until ALT and AST ≤3 × ULN or they return to baseline Resume ceritinib with 150 mg dose reduction Discontinue ceritinib indefinitely
		ALT ≥3 × ULN or AST ≥5 × ULN and total bilirubin ≥2 × ULN in absence of cholestasis or hemolysis	

ALT: alanine transaminase; AST: aspartate transaminase; BG: blood glucose; bpm: beats per minute; CHF: congestive heart failure; ECG: electrocardiogram; HR: heart rate; LFTs: liver function test; QTc: corrected QT interval; ULN: upper limit of normal.

Alectinib

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Alectinib

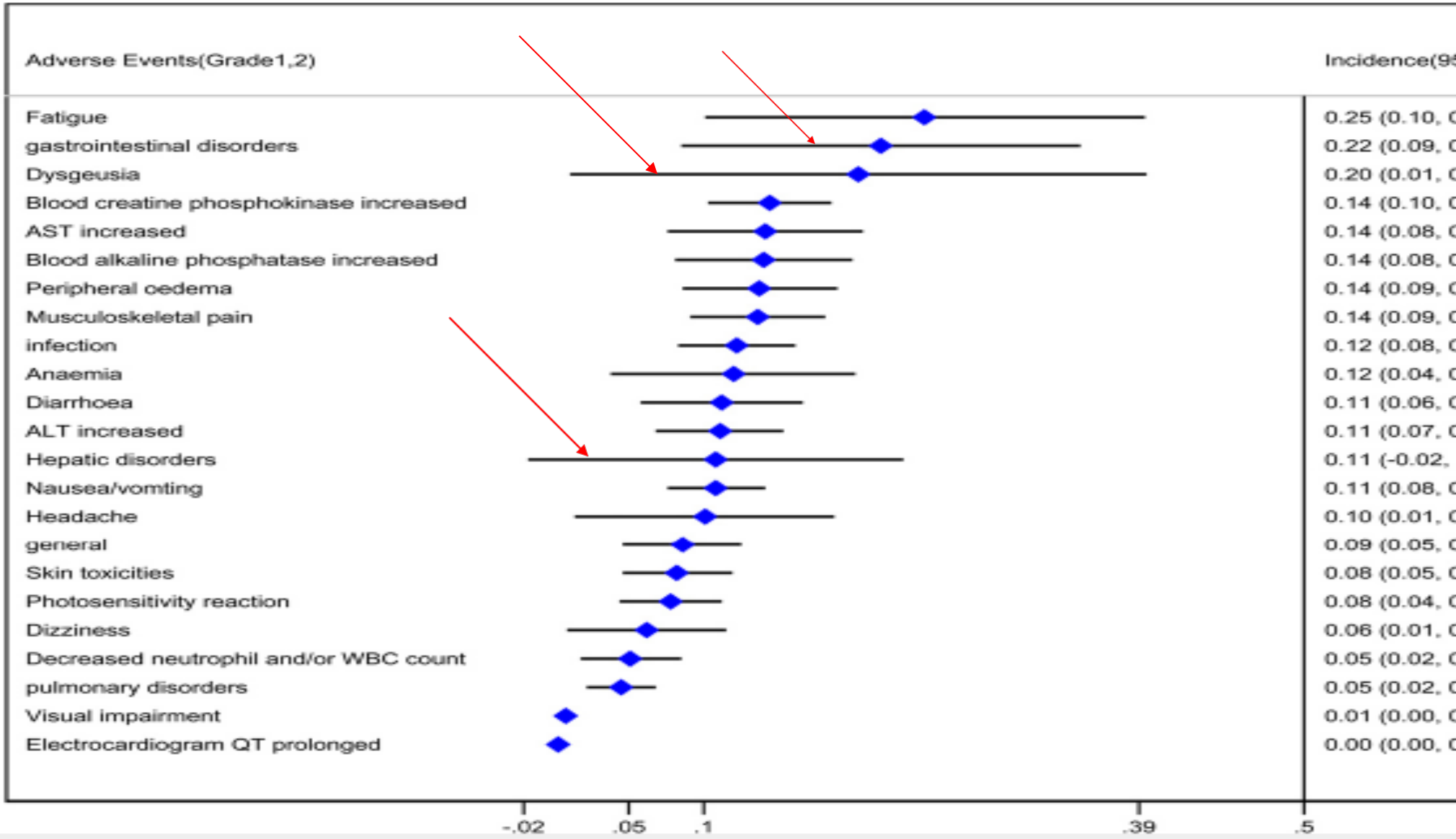
- **Main Adverse events:**
- Hematological: anemia (20%),
- Vascular: peripheral edema(17%),
- Musculoskeletal: myalgia (16%),
- Hepatic: increased ALT (15%), increas AST (14%), increased blood bilirubin(15%)
- Gastrointestinal: nausea (14%), and diarrhea (12%).
- Others: gained weight
- The most common grade 3–5 adverse events were anemia (5%), increased A (5%), and increased AST (5%)

Table 3. Safety Overview and Adverse Events of Any Grade That Differed by 5 Percentage Points or More in Frequency between Groups.*

Event	Crizotinib (N=151)		Alectinib (N=152)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)			
Adverse event	146 (97)	76 (50)	147 (97)	63 (41)
Serious adverse event	—	44 (29)	—	43 (28)
Fatal adverse event†	—	7 (5)	—	5 (3)
Adverse event leading to treatment discontinuation	19 (13)	—	17 (11)	—
Adverse event leading to dose reduction	31 (21)	—	24 (16)	—
Adverse event leading to dose interruption	38 (25)	—	29 (19)	—
Adverse events that differed by ≥5 percentage points in frequency between groups				
Nausea	72 (48)	5 (3)	21 (14)	1 (1)
Diarrhea	68 (45)	3 (2)	18 (12)	0
Vomiting	58 (38)	5 (3)	11 (7)	0
ALT increased	45 (30)	22 (15)	23 (15)	7 (5)
AST increased	37 (25)	16 (11)	21 (14)	8 (5)
Blood bilirubin increased	2 (1)	0	23 (15)	3 (2)
Weight increased	0	0	15 (10)	1 (1)
γ-Glutamyltransferase increased	10 (7)	2 (1)	1 (1)	1 (1)
Peripheral edema	42 (28)	1 (1)	26 (17)	0
Dizziness	21 (14)	0	12 (8)	0
Dysgeusia	29 (19)	0	4 (3)	0
Visual impairment	18 (12)	0	2 (1)	0
Vision blurred	11 (7)	0	3 (2)	0
Photopsia	9 (6)	0	0	0
Myalgia	3 (2)	0	24 (16)	0
Musculoskeletal pain	3 (2)	0	11 (7)	0
Anemia	7 (5)	1 (1)	30 (20)	7 (5)
Alopecia	11 (7)	0	1 (1)	0
Photosensitivity reaction	0	0	8 (5)	1 (1)

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† Two events in the crizotinib group and none in the alectinib group were reported to be related to the trial treatment.

Alectinib



Ann Palliat Med 2020;9(4):1782-1796 | http://dx.doi.org/10.21037/apm-19-643

Alectinib

Categorizing side effects

Gastrointestinal impartment:

1. Diarrhea
2. Nausea
3. Vomit

Diarrhea/Management:

1.. Target therapy teaching

2. May appear first 2 weeks after therapy

3. To take loperamide with diarrhea #1 (2 tablets each episode/no more than 10 daily)

4. If loperamide does not help to add Diphenoxylate and atropine 2 tablets x 4 times

5. Prevent to get dehydrated

6. Dietary recommendations

7. You may held medication until diarrhea resolved and restart with dose reduction

Constipation/ Management:

1. Increased fluid intake
2. Recommended exercise
3. Drink prune juice
4. Take surfactant (docusate sodium), stimulant laxative (Senna), etc.

Vomiting:

1. Try ginger
2. Treat with 5-HT3 antagonist (ondasetron)

Musculoskeletal pain:

Myalgia

Managed pain with OTC acetaminophen or NSAID'S

:

Labs changes:

1. Anemia
2. Elevated LFT's
3. Hyperbilirubinemia

To check CBC, CMP once a month

If LFT's are elevated 3 x times form VNL , to hold medication . Resume with dose reduction.

Recommended enriched iron diet + folic acid OTC supplement

Physical symptoms:

1. Increase weight
2. Peripheral edema

Recommended patient to exercise, keep a balance diet

To decrease peripheral edema recommended to elevate legs above the level of the heart, exercise, wear compression stockings and reduce salt intake.

Summary:

The most frequent side effects are GI symptoms, musculoskeletal discomfort, gain weight , peripheral edema and changes in the labs such as anemia and elevated LFT's including bilirubin

Brigatinib

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Brigatinib

Main Adverse events:

Hepatic: grade 3 increased alanine aminotransferase, pancreatic enzymes elevation

IDL/Pneumonitis: Cough (39%) , dyspnea (first week of therapy)

Gastrointestinal: nausea (53%), diarrhea (41%),

General: fatigue (43%), headache

Cardiovascular: HTN: check first 2 weeks/then every 4 weeks

Visual disturbance: check with ophthalmologist. If affect ADL's , do dose reduction

Myositis: CPK elevation

CHECK: LFT'S, AMYLASE, LIPASE AND CPK.

EKG as baseline.

Table 3 AEs observed with brigatinib, alectinib, and ceritinib

	Most common AEs	Most common G3–4 AEs	G3–4 AEs	Serious AEs	Discontinuation due to AEs	Dose reduction due to AEs	Treatment-related deaths
Brigatinib							
Phase I/II[15]	Nausea (53%) Fatigue (43%) Diarrhea (41%)	↑ Lipase (9%) Dyspnea (6%) Hypertension (5%)	64% (36% TR)	Dyspnea (7%) Pneumonia (7%) Hypoxia (5%)	9%	15%	3 Sudden death Hypoxia Unknown cause
Phase II[17]	Nausea (40%) Diarrhea (38%) Cough (34%)	↑ CPK (8%) Hypertension (5%) Pneumonia (5%)	n/a	n/a	8%	20%	n/a
Alectinib							
Phase II global[24]	Constipation (33%) Fatigue (26%) Peripheral edema (25%)	Dyspnea (3%) Fatigue (1%) Headache (1%)	n/a	n/a	8%	21%	1 Intestinal perforation
Phase II single group[23]	Constipation (36%) Fatigue (33%) Myalgia (24%)	↑ CPK (8%) ↑ ALT (6%) ↑ AST (5%)	n/a	15%	2%	16%	1 Hemorrhage
Ceritinib							
Phase I[25]	Diarrhea (86%) Nausea (81%) Vomiting (61%)	↑ ALT (30%) Diarrhea (6%) Hyperglycemia (6%)	81% TR (51%)	48% TR (12%)	11%	62%	2 ILD Ischemic hepatitis
Phase II[26]	Nausea (81%) Diarrhea (80%) Vomiting (63%)	n/a	n/a	n/a	8%	n/a	n/a

Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ILD, interstitial lung disease; n/a, not available; TR, treatment related; G3–4, grades 3–4.

Brigatinib: Categorizing side effects

Gastrointestinal impairment:

1. Diarrhea
2. Nausea
3. Vomit

- Management of diarrhea
- Hold medication if diarrhea is refractory to therapy
- Reinitiate therapy with drug reduction

Pneumonitis:

- Cough
- Shortness of breath
- FIRST WEEK.

- If patient develop pneumonitis Brigatinib should be discontinued permanently

Physical symptoms:

1. Hypertension: follo
every 2 weeks for the
months, then every 4 w

Blood pressure should be m
Daily log by patient /caregi
Start patient on BP medicati
Monitor weekly until BP
controlled
EKG as baseline : may
changes on QTc

Lorlatinib

Lorlatinib

Main Adverse events:

Symptoms: peripheral edema, weight gain, peripheral neuropathy, cognitive effects,

Gastrointestinal: diarrhea

IDL/pneumonitis: dyspnea

Lipid disorder: Hypercholesterolemia hypertriglyceridemia.

Serious adverse events (34%): pneumonia, dyspnea, respiratory failure, cognitive effects, and pyrexia.

CHECK: LIPID PANEL

Table 1. Adverse reactions in ≥10% of all patients or Grade ≥3 adverse reactions in any patient treated with lorlatinib 100 mg once daily

Adverse drug reactions, *n* (%)	Pooled lorlatinib 100 mg once daily (*N* = 295)		
	All grades	Grade 3	Grade 4
Hypercholesterolemia[a]	243 (82.4)	41 (13.9)	5 (1.7)
Hypertriglyceridemia[a]	179 (60.7)	39 (13.2)	7 (2.4)
Edema[a]	151 (51.2)	7 (2.4)	0 (0.0)
Peripheral neuropathy[a]	129 (43.7)	7 (2.4)	0 (0.0)
Cognitive effects[a]	68 (23.1)	5 (1.7)	0 (0.0)
Fatigue[a]	68 (23.1)	1 (0.3)	0 (0.0)
Mood effects[a]	62 (21.0)	4 (1.4)	0 (0.0)
Weight increase	61 (20.7)	7 (2.4)	0 (0.0)
Arthralgia	58 (19.7)	0 (0.0)	0 (0.0)
Diarrhea	52 (17.6)	2 (0.7)	0 (0.0)
Constipation	42 (14.2)	0 (0.0)	0 (0.0)
Vision disorder[a]	39 (13.2)	1 (0.3)	0 (0.0)
Speech effects[a]	28 (9.5)	1 (0.3)	0 (0.0)

[a]Clustered term comprising adverse events that represent similar clinical symptoms/syndromes.
Based on Common Terminology Criteria for Adverse Events (v4.03).

Lorlatinib: Categorizing side effects

Hyperlipidemia:

Hypercholesterolemia: onset 4 weeks after starting lorlatinib

Treatment:

1. Atorvastatin
2. Rosuvastatin
3. Pitavastatin

Hypertriglyceridemia: onset 4 weeks after starting lorlatinib

Treatment:

1. Omega 3 fatty acid
2. Ezetimibe
3. Phenofibrate

Cognitive effect:

Hallucinations: early onset (days after staring lorlatinib)

If persist dose hold, rarely needs dose reduction

Impulse Control: more frequent if history of CNS radiation therapy.

Avoid high stress (work/personal)

Treatment:

1.Pshychology/psychiatrist therapy

2. If persistent permanent drug reduction

Personality changes: high risk with age and history of CNS radiation therapy

Treatment:

1. Permanent drug reduction

Mood effect:

Depression/ suicidal ideation: discuss with patient before starting therapy, very rare occurrence. There is not documentation of any suicide attempt

Euphoria: will be increase on appetite and weight gain

Does not require dose modification

Recommend patient to exercise and have a balance diet

Physical symptoms:

Edema/weight gain: months a stating lorlatinib (20% of base weight)

To decrease edema:

1. Compression stockings
2. Elevated legs above level o
3. Exercise
4. Decrease salt intake

Hold dose for no more than 14 or dose reduction

Peripheral Neuropathy: onse usually weeks or months after lorlatinib

Mainly on wrist, joints

Treatment: dose reduction for 14 days

Management of toxicities from ALK inhibitors

Gastrointestinal toxities: nausea, vomit, diarrhea (crizotinib/ceritinib)

Elevated LFT's: transaminase elevation (crizotinib/ceritinib) and brigatinib

Pulmonary toxicity: crizotinib, ceritinib, brigatinib and alectinib

Visual toxicity: crizotinib

Neurological toxicity: lorlatinib

Endocrine toxicity: crizotinib

Photosensitivity reactions: brigatinib

Cardiac toxicity: crizotinib, ceritinib and brigatinib. EKG as baseline.

HTN: brigratinib

Musculoskeletal toxicity: alectinib and brigatinib

Metabolic toxicity: crizotinib, lorlatinib, cerinibib (metabolized by P450 3A4 (CYP3A4)

Hypercholesterolemia: lorlatinib (rosuvastatin/pravastatin)

Hypertriglyceridemia: fibrates

Bruton tyrosine kinase (BTK) inhibitor

B-cell receptor pathway has been linked to the development and maintenance of B-cell malignancies

It is a protein early in this pathway

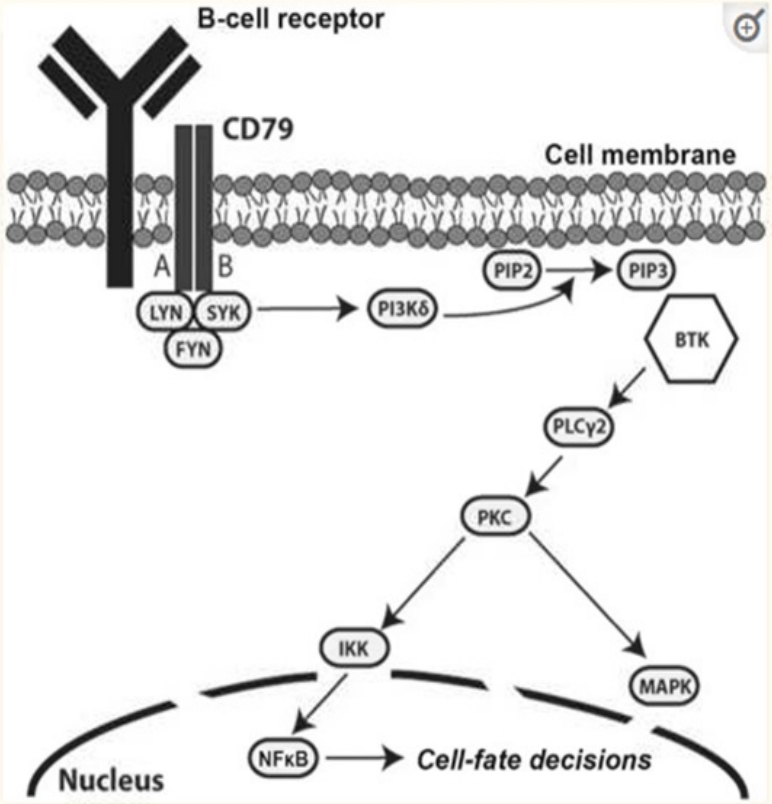


Figure 1.

The B cell receptor signalling pathway controls B-cell fate and function. Reprinted from Aalipour and Advani [2013] with permission from Wiley. BTK, Bruton's tyrosine kinase; IKK, IκB Kinase MAPK, mitogen-activated protein kinase; NFκB, nuclear factor κB; PI3Kδ, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5 bisphosphate; PIP3, phosphatidylinositol 3,4,5 triphosphate; PKC, protein kinase C; PLCγ2, phospholipase C γ2.

Bruton tyrosine kinase (BTK) Inhibitor

Ibrutinib

Main adverse events:

Hematological: Hemorrhage, cytopenias, tumor lysis syndrome

Non Hematological: infections, cardiac arrhythmias, HTN, second primary malignancy (non skin carcinoma

In patients with B cell malignancy:

Hematological: thrombocytopenia, neutropenia 38 %, anemia 35%, bruising 32%

Non Hematological:, diarrhea 43.8%, fatigue 39.%, musculoskeletal pain ,, rash 35%, HTN

Grade 3 or more:

Hematological: neutropenia 20.7 % thrombocytopenia 13.6%

Non hematological: pneumonia 8.2 % and HTN 8%

In patients with BVHD are fatigue, bruising, diarrhea, thrombocytopenia, muscle spasm, stomatitis, nausea, hemorrhage, anemia and pneumonia

Monitor for bleeding, infections, cardiac arrhythmias, HTN, check his CBC once a month.

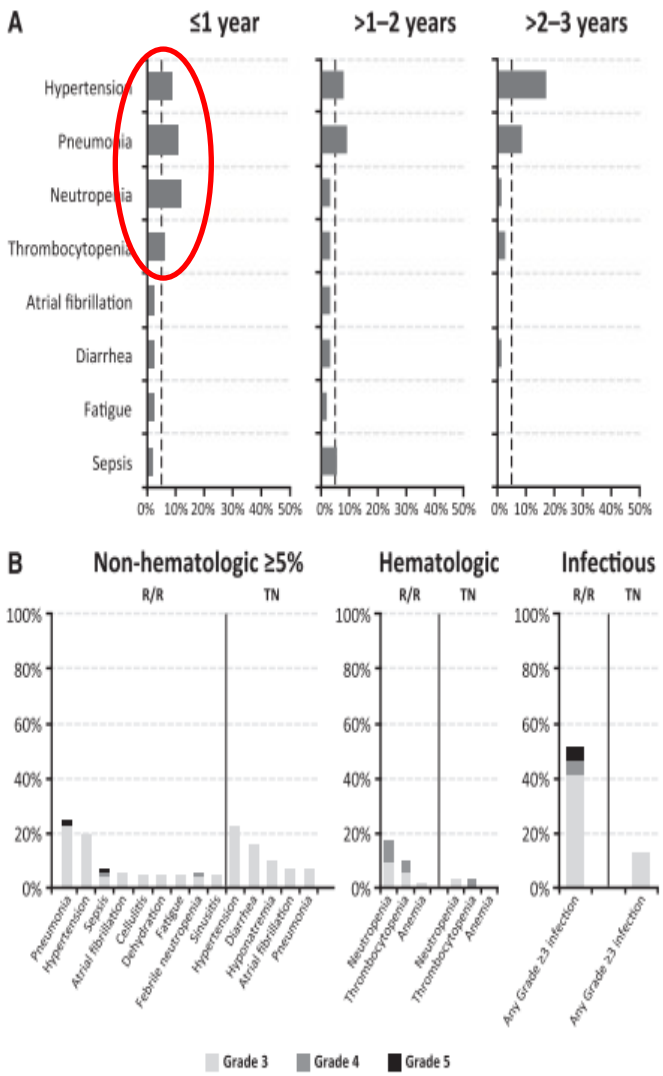


Figure 1. Serial assessment of adverse events over time. (A) Grade ≥3 AEs by time to event onset from first dose date. The dashed line denotes a 5% rate; x-axis maximum is 50%. (B) Frequency of grade ≥3 AEs by TN or R/R status.

Ibrutinib

Categorizing side effects

Hematologic impairment:	**Non-Hematologic impairment:**	**B cell malignancies (MCL, CLLSLL,WM and MZL) and Ibrutinib:**	**cGVHD and ibruitinib:**	Management:
1.Citopenias: neutropenia, anemia, thrombocytopenia	1. Hypertension	1. Diarrhea	1. Fatigue	**Hematological impairment:**
2.Increase risk for infections (pneumonia, sepsis, cellulitis, febrile neutropenia)	2.Atrial fibrillation	2. Fatigue	2.Bleeding: Hematomas	Hold Ibrutinib
	3. Dehydration	3.Muskuloskeletal despair(myalgia, arthritis)	3. Diarrhea	1. Treat neutropenia
	4.Electrolyte imbalance	4. Skin changes : rash	4. Stomatitis	Hold dose, recheck a week later.
	5.TumorLysis Syndrome (TLS)	5.Bleeding: Hematomas	5. Myalgia	2. Treat Anemia
	6.Second primary malignancies		6. Nausea	3. Treat infections until solved
			7. Increase risk for infections: pneumonia	**Non-Hematological impairment:**
				1. Treat HTN
				2. Any life threatening arrhythmia should be d/c
				3.Treat diarrhea/dehydration/electrolyte imbalance (reduce dose)
				4. TLS (discontinue)
				5. Secondary primary malignancies (discontinue)

Bruton tyrosine (BTK)inhibitor

Acalabrutinib

Main Adverse events:

Hematological: anemia 37% and grade 3 15%, bruise , hemorrhage, neutropenia 13-48%, grade 3 23%, thrombocytopenia 33%

Non hematological: Skin rash (9% to 25%), Increased uric acid (15% to 22%), GI disturbances (15-20%), and grade 3 7%., LFT's elevation 15-20%, infection 65% with grade 3 19%. Muscle pain 32%, respiratory infection 18-33%

Enhance anticoagulant effect. Avoid PPI's.

CHECK: EKG as baseline, CBC AND CMP every 4 weeks, Hemorrhages and infections

ASCEND: Safety

Most Common AEs, n (%)	Acalabrutinib (n = 154)		IdR (n = 118)		BR (n = 35)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
Headache	34 (22)	1 (1)	7 (6)	0	0	0
Neutropenia	30 (19)	24 (16)	53 (45)	47 (40)	12 (34)	11 (31)
Diarrhea	28 (18)	2 (1)	55 (47)	28 (24)	5 (14)	0
Anemia	23 (15)	18 (12)	11 (9)	8 (7)	4 (11)	3 (9)
Cough	23 (15)	0	18 (15)	1 (1)	2 (6)	0
Pyrexia	19 (12)	1 (1)	21 (18)	8 (7)	6 (17)	1 (3)
Fatigue	15 (10)	2 (1)	10 (8)	0	8 (23)	1 (3)
Nausea	11 (7)	0	15 (13)	1 (1)	7 (20)	0
IRR	0	0	9 (8)	2 (2)	8 (23)	1 (3)
AEs of clinical interest for acalabrutinib						
Atrial fibrillation	8 (5)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Bleeding	40 (26)	3 (2)	9 (8)	3 (3)	2 (6)	1 (3)
Hypertension	5 (3)	3 (2)	5 (4)	1 (1)	0	0
SPM (no NMSC)	10 (6)	5 (3)	3 (3)	0	1 (3)	1 (3)

Ghia. EHA 2019. Abstr LB2606.

Slide credit: clinicaloptions.com

Acalabrutinib: Categorizing side effects

Non- Hematological impairment:

1. Gastrointestinal:
1. Diarrhea
2. Infections: Upper and lower respiratory tract infection
3. Skin rash
4. Headache
5. Hemorrhage
6. Myalgia
7. Fatigue
8. Increase uric acid (check once a month)

Hematological impairment:

1. Anemia
2. Neutropenia
3. Thrombocytopenia
4. Lymphocytosis
5. Enhance anticoagulants effect

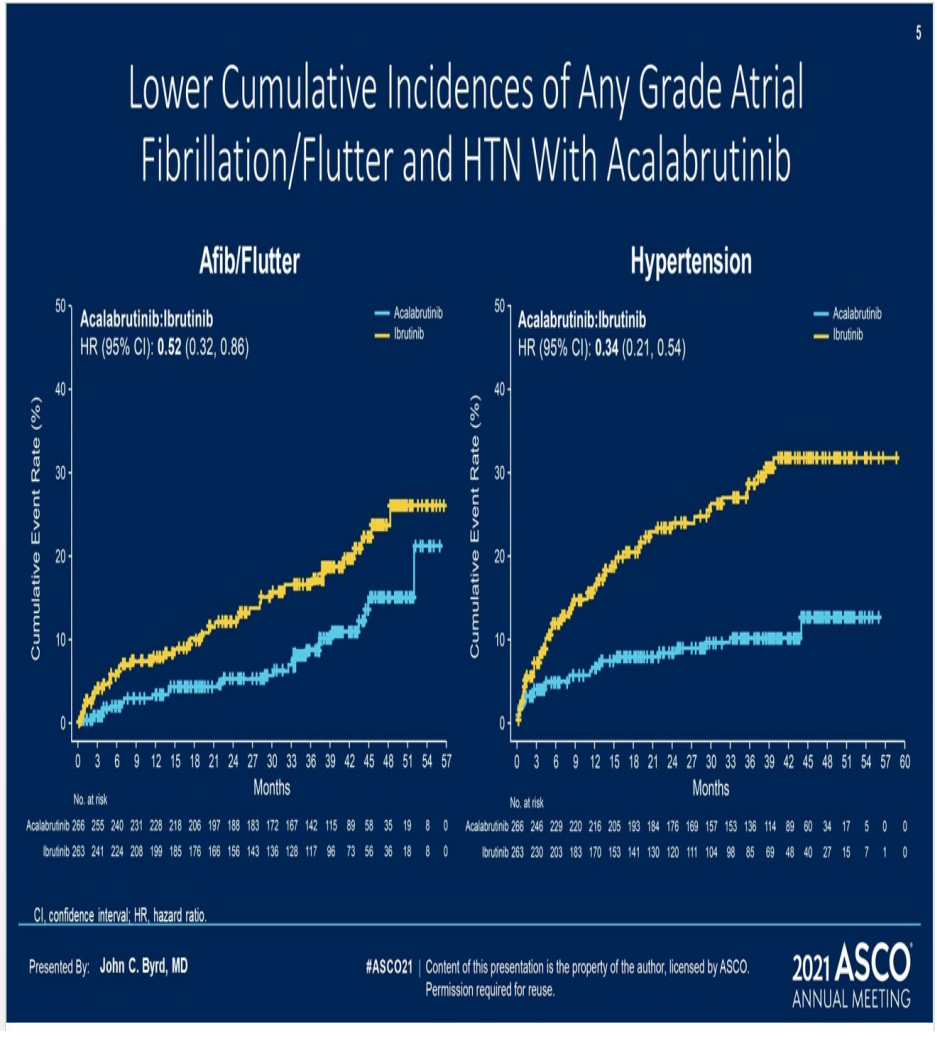
Check first months every 2 weeks then every 4 weeks

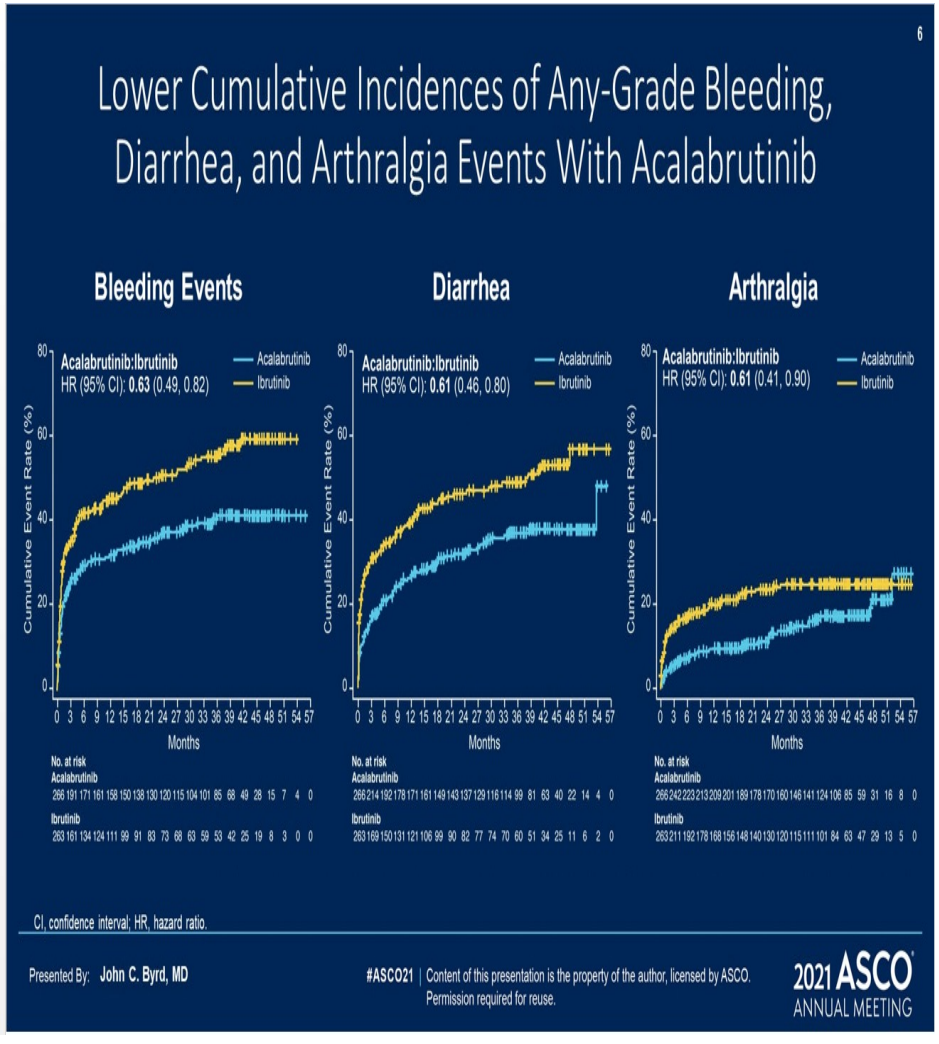
What to do?

1. Treat diarrhea. Reinitiat same dose.
2. Skin rash: treated with topical steroids. If infected topical antibiotics.
3. Bleeding: hold medication. Reinitiated wi drug reduction 100 mg by mouth daily

If grade IV cytopenias discontinue

Acalabrutinib vs Ibrutinib





ELEVATE CLL R/R: Phase 3 Randomized Non-inferiority Open-Label Trial

Bruton tyrosine (BTK) inhibitor

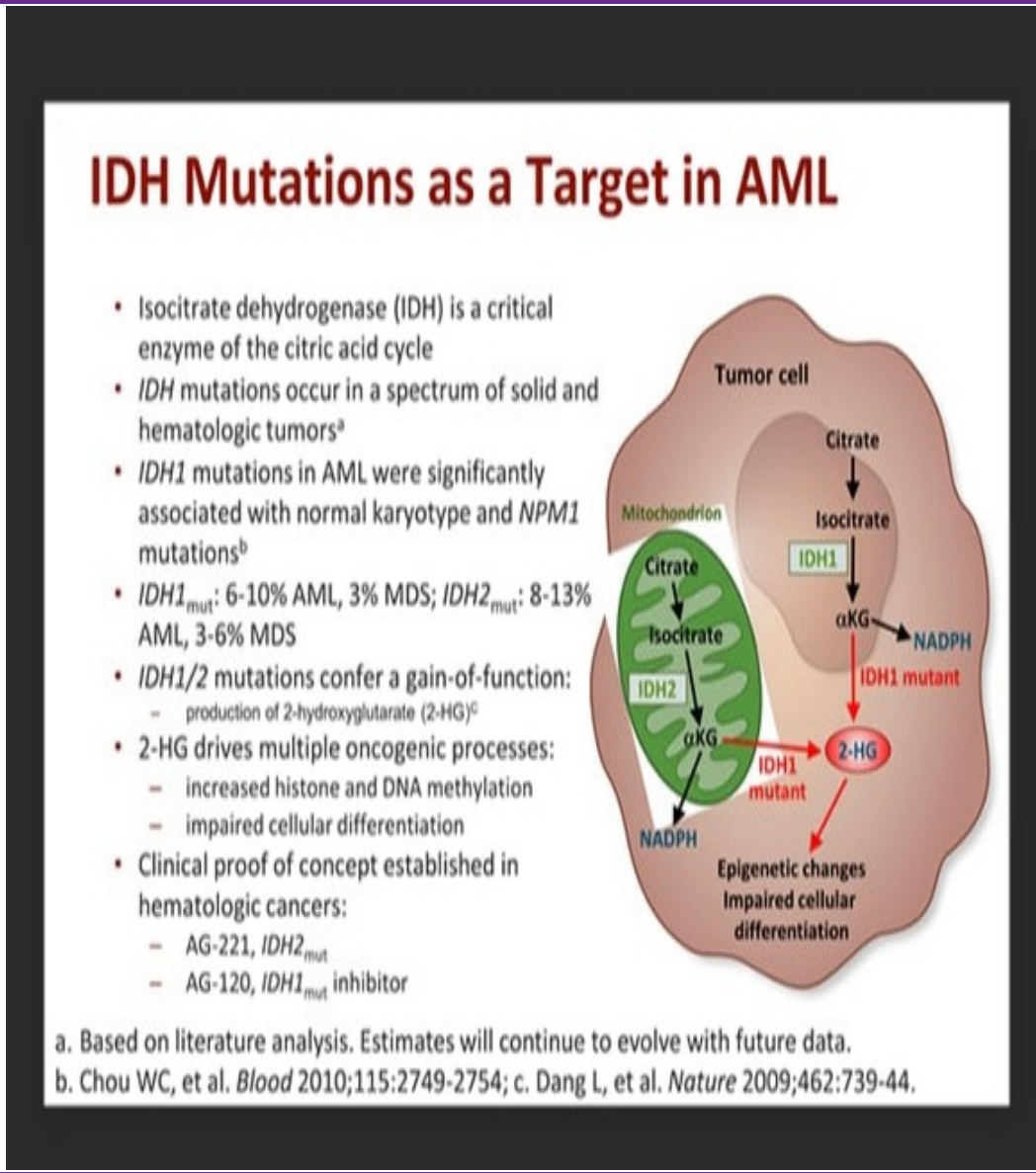
	Acalabrutinib				Ibrutinib			
	R/R MCL (23, 24)	R/R CLL (22)	TN & R/R WM[a] (25, 26)	TN CLL (21)	R/R MCL (9)	R/R CLL (end of trial/long-term follow-up) (27, 28)	R/R WM (29)[a]	TN CLL (end of trial/long-term follow-up) (12, 30)
Number of patients	*124*	*155*	*106*	*179/179[b]*	*111*	*195/195*	*63*	*136/136*
Median duration of treatment (range), months	*17.3 (0.1–35.1)*	*15.7 (1.1–22.4)*	*N/A*	*27.7 (IQR 25.0–32.8)/ (IQR 24.8–33.0)*	*N/A*	*8.6 (0.2–16.1)/ 41.0 (0.2–71.1)*	*19.1 (0.5–29.7)*	*17.4 (0.7–24.7)/ 57.1 (0.7–66.0)*
Median duration of follow-up (range), months	*26.3 (0.3–35.1)*	*16.1 (0.03–22.4)*	*27.4 (IQR 26.0–29.7)*	*28.3 (IQR 25.6–33.1)*	*15.3 (1.9–22.3)*	*9.4 (0.1–16.6)/ 65.3 (0.3–71.6)*	*N/A*	*18.4/60 (0.1–66)*
Adverse events (all grades unless otherwise stated)								
Headache	38%	22%	39%	40%/37%	N/A (<15%)	N/A/21%[c]	2%	N/A/N/A
Nausea	19%	7%	23%	20%/22%	31%	G1 24%, G2 6%, G3 2%/36%[c]	N/A	22%/26%
Diarrhea	36%	18%	33%	39%/35%	50%	G1 27%, G2 10%, G3 4%/62%[c]	3%	42%/50%
Fatigue	28%	10%	22%	28%/18%	41%	G1 18%, G2 12%, G3 3%/42%[c]	N/A	30%/36%
Peripheral edema	N/A	N/A	N/A	12%/9%	28%	N/A/24%[b]	N/A	19%/27%
Myalgia	21%	N/A	N/A	N/A	N/A (<15%)	N/A/N/A	N/A	N/A/N/A
Neutropenia	10%	19%	17%	32%/11%	18%	G3 18%/31%[c]	22%	16%/13%[d]
Bleeding events	33%	26%	58%	43%/39%	N/A	N/A/N/A	6%	N/A/N/A
Grade ≥3	2%	1%	3%	2%/2%	5%	N/A/N/A	N/A	N/A/N/A
Cardiac events (all)	10%	N/A	N/A	N/A	N/A	N/A/N/A	N/A	N/A/N/A
Atrial fibrillation	0	5%	5%	3%/4%	N/A	7%/12%	5%	6%/16%
Hypertension	3%	3%	N/A	3%/2%[b]	N/A	N/A/21%	5%	4%[b]/26%
Infections (all)	53%	N/A	N/A	N/A	N/A	N/A/N/A	N/A	N/A/N/A
Grade ≥3	15%	15%		21%/14%	25%	N/A/46%	N/A	N/A/N/A
Discontinuation due to adverse events	8%	11%	7%	11%/9%	7%	7%/16%	10%	9%/28%

IDH inhibitor

Mutations in isocitrate dehydrogenase genes (IDH1 and IDH2)

The IDH family of enzymes comprises three proteins located in the cytoplasm and peroxysomes (IDH1) and mitochondria (IDH2 and IDH3), which are involved in a number of cellular processes.

30% Acute Myeloid leukemia (AML)



Ivosidenib

Stronger Together

Ivosidenib

IDH-1 INHIBITOR

Main Adverse events are:

Hematological:

Differentiation syndrome: steroids (3 days minimum),non infectious leukocytosis(tx with hydroxyurea/leukapheresis)

Non Hematological: prolonged QTc (monitor electrolytes),Guillain-Barre Syndrome(d/c)

Grade ≥3 Adverse events (≥5 percent)

Differentiation syndrome (DS); which can be fatal if not treated promptly) (dyspnea, fever, peripheral edema, hypotension, weight gain, pleuro-pericardial effusion, acute renal failure, musculoskeletal pain, and hyperbilirubinemia)

Prolonged QTc interval, and fatigue; and Guillain-Barré syndrome .

CHECK : EKG, CBC,CMP(electrolytes, LFT's, glucose, calcium), magnesium, phosphorus, uric acid.

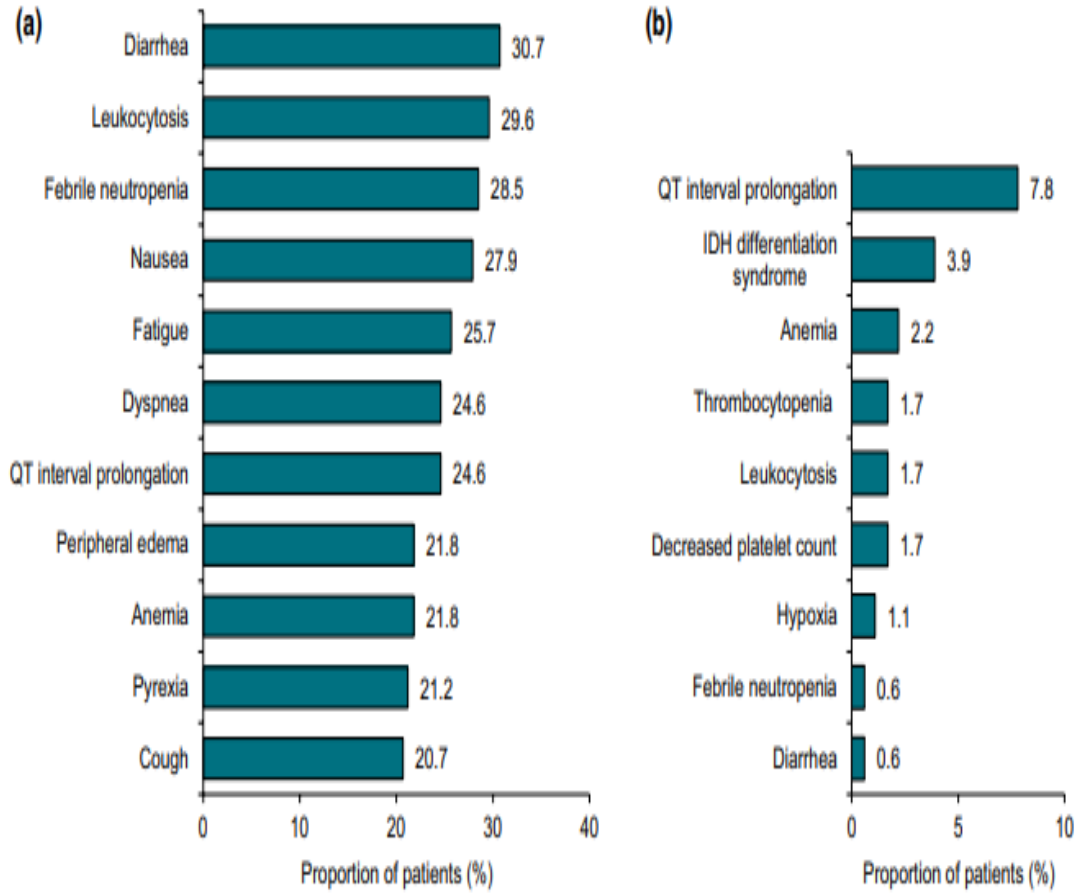


Fig. 1 Tolerability of ivosidenib in the treatment of *IDH1* mutation-positive relapsed or refractory acute myeloid leukemia in the safety population of 179 patients receiving a starting dosage of 500 mg once daily in the phase 1 trial [21]: **a** treatment-emergent adverse events reported in ≥ 20% of patients; **b** grade 3/4 treatment-related adverse events as assessed by the investigator. *IDH* isocitrate dehydrogenase

Ivosidenib

Categorizing side effects

Non Hematological impairment:

Arrhythmias :

QTC interval prolongation

1. 480 msec to 500 msec: hold. Restart QTC interval return to less then or equal to 480 msec (EKG every 2 weeks). Resume dose will be 500 mg po daily

2. > 500 msec: hold. Resume dose will be 250 mg once daily with QTC at least 480 msec (ECGs at least weekly for 2 week)

Life threatening arrhythmia : Discontinue

MUST DO:

ECG as baseline. Weekly for first 3 weeks, then at least once a month for the duration of therapy

Check electrolytes (Mg, Calcium/ treated

HTN : Manage HTN. Monitor closely

Respiratory impairment:

Dyspnea. Check closely only 2% may develop grade 3

Non hematological impairment:

Guillain-Barre Syndrome:

less than 1%

Check:

unilateral/bilateral weakness, sensory alterations, paresthesia or difficulty breathing.

Permanently discontinue

Differentiation syndrome: dyspnea, fever, peripheral edema, hypotension, weight gain, pleuro-pericardial effusion, acute renal failure, musculoskeletal pain, and hyperbilirubinemia

TREATMENT WITH STEROIDS (3 DAYS MINIMUM)

Gastrointestinal impairment:

Abdominal pain, diarrhea, nausea, vomiting, mucositis

CHECK LFT's

Psychiatric impairment:

insomnia

Others:

Arthralgia, headaches, skin rash, peripheral edema

Hematological impairment:

Cytopenias: Anemia, neutropenia, thrombocytopenia,

lymphocytosis (treatment with hydroxyurea/leukapheresis), taper hydroxyurea only afterleukocytois improves or resolves. Interrupt ivosidenib if leukocytosis does not improved. If resolved restart 500 mg po daily

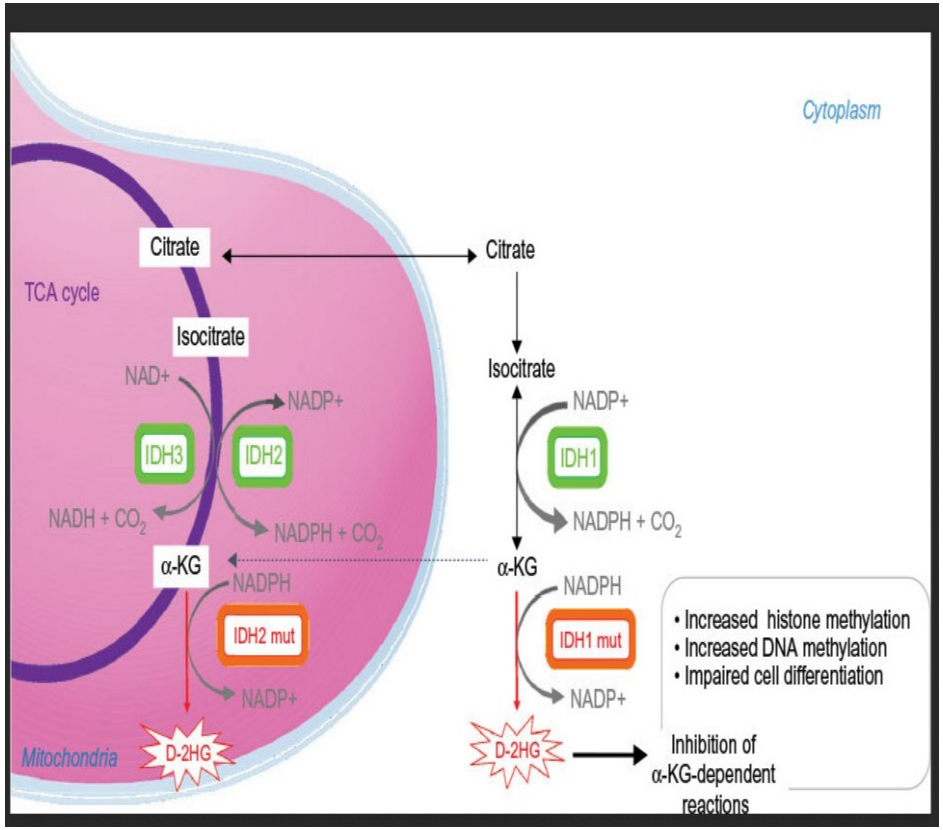
AML monotherapy:

Interrup ivosidenib until toxicity resolved to grade 2 or lower'reinitiate at 250 mg po daily, may increase to 500 mg daily if toxicities resolved to grade 1

AML combination: Ivosidenib + azacitidine: hold both medications. Resume grade 3(500 mg daily), grade 4 (250 mg po daily)

IDH2 inhibitor

- isocitrate dehydrogenase-2 inhibitor (IDH2) inhibitor
- Spur the synthesis of 2-HG, a metabolite that prevents myeloid cells from differentiating and drives the development of the cancer
- Occur in up to 19% of patients with AML
- Older patients
- IDH2 are more common than IDH1 mutations
- Detected by molecular profiling



IDH2 inhibitor

Enadisenib

Adverse events:

Hematological: non infectious leukocytosis

Non Hematological:

Gastrointestinal: nausea, diarrhea, vomiting, elevated bilirubin (greater than 3 times)and decreased on appetite

Grade ≥3 adverse reactions in ≥5 percent of patients include diarrhea, nausea, and Differentiation Syndrome (DS) 7% (which can be fatal if not treated promptly).

CHECK: CBC,CMP, LFT's

Table 2.

Treatment-related TEAEs of grades 3 or 4 occurring in ≥2% of all patients

TEAE	Enasidenib 100 mg per day (n = 153)		All patients (N = 239)	
	No.	%	No.	%
Hyperbilirubinemia*	13	8	29	12
IDH differentiation syndrome†	11	7	15	6
Anemia	10	7	12	5
Thrombocytopenia‡	8	5	15	6
Tumor lysis syndrome	5	3	8	3
Decreased appetite	3	2	6	3
Leukocytosis	2	1	6	3
Fatigue	2	1	6	3
Nausea	2	1	5	2
Lipase increased	2	1	5	2

A treatment-related TEAE was defined as any event that began or worsened on or after the start of enasidenib use until 28 days after the last dose and was considered by the treating physician to be possibly or probably related to enasidenib. TEAEs were coded by using the Medical Dictionary for Regulatory Activities, version 16.0.

* Includes the preferred terms "hyperbilirubinemia" and "blood bilirubin increased."

† Preferred term is "retinoic acid syndrome."

‡ Includes the preferred terms "thrombocytopenia" and "platelet count decreased."

https://doi.org/10.1182/blood-2017-04-779405

Enasidenib: Categorizing side effects

Non Hematological impairment:

Gastrointestinal impairment:

Diarrhea, nausea, vomiting

Decreased appetite

Differentiation Syndrome:

Treatment with systemic corticosteroids. Hold enasidenib if severe pulmonary/renal impairment

Resume when signs/symptoms improve to grade 2 or lower.

Hematological impairment:

Non infectious leukocytosis:

Treatment with hydroxyurea. HOLD enasidenib if there is not improvement with tx. Resume when WBC is less than 30 x 10(9)/L

Changes in labs:

Leukocytosis (CBC every 2 weeks for the first 3 months)

Hypokalemia: treated

Elevated bilirubin greater than 3 times the ULN(2 weeks), Normal transaminases: Dose reduction to 50 mg po daily

To Take Home

- ALK inhibitor: once a month visit with CBC, CMP, lipid panel (lorlatinib), EKG baseline (Brigatinib)
- BTK inhibitor:EKG as baseline, CBC AND CMP every 4 weeks, Hemorrhages and infections (mainly pneumonia)
- IDH1/IDH2 inhibitor:: EKG, CBC,CMP(electrolytes, LFT's, glucose, calcium), magnesium (IDH1), phosphorus(IDH1), uric acid (IDH1).
- DS (which can be fatal if not treated promptly).
- Close monitoring is very important

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